In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 15-1016V
Filed: June 2, 2020
PUBLISHED

MARYELLEN KOTTENSTETTE and NICHOLAS KOTTENSTETTE, as best friends of their daughter (CK),

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Decision on Remand; Infantile Spasms; DTaP Vaccination; *Althen* Prong Two

John F. McHugh, Law Office of John McHugh, New York, NY, for petitioners.
Camille Michelle Collett, U.S. Department of Justice, Washington, DC for respondent.

DECISION ON REMAND[1]

On September 11, 2015, petitioners, Maryellen and Nicholas Kottenstette, filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012), alleging that their minor daughter, C.K., suffered an encephalopathy following several vaccinations administered on October 2, 2012.[2] (ECF No. 1, pp. 1-2.) Petitioners alleged C.K.'s encephalopathy represented a Table Injury following her DTaP vaccination or, alternatively, that it was caused-in-fact by her October 2, 2012 DTaP vaccination. (*Id*. at 4-5.) However, they later pursued this case on the basis that C.K. experienced infantile spasms caused-in-fact by her October 2, 2012 vaccinations, including most notably her DTaP vaccination.

[1] Because this decision contains a reasoned explanation for the special master's action in this case, it will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. *See* 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to redact medical or other information the disclosure of which would constitute an unwarranted invasion of privacy. If the special master, upon review, agrees that the identified material fits within this definition, it will be redacted from public access.

[2] Specifically, Diphtheria, Tetanus, and acellular Pertussis ("DTaP"), Haemophilus influenzae b ("Hib"), inactivated polio ("IPV"), and pneumococcal conjugate ("PCV") vaccines.

The previously-assigned special master found petitioners entitled to compensation (2017 WL 6601878 (Fed. Cl. Spec. Mstr. Dec. 12, 2017)) and later issued a decision awarding damages (2019 WL 2587395 (Fed. Cl. Spec. Mstr. May 29, 2019)). Although this case was not reassigned to me until after the decision awarding damages was issued, the prior ruling on entitlement was subsequently vacated upon respondent's motion for review and the case was remanded to me by the Court of Federal Claims for further consideration of petitioners' entitlement to compensation consistent with the *Althen* test for causation-in-fact. 2020 WL 953484 (Fed. Cl. Feb. 12, 2020). For the reasons set forth below, I conclude that petitioners are not entitled to compensation because they have not met their burden under the second *Althen* prong of demonstrating a logical sequence of cause and effect establishing that C.K.'s condition, diagnosed as infantile spasms, was caused by vaccination.

I. Procedural History

At the initial status conference held on November 20, 2015, the special master explained that C.K.'s injury was unlikely to represent a Table encephalopathy (*see also* Section VII, below), but encouraged the parties to explore settlement based on an injury of infantile spasms. (ECF No. 14.) Subsequently, in August of 2016, petitioners filed an expert report opining that C.K. experienced vaccine-caused infantile spasms. (ECF No. 19; Ex. 6.) Since that time, this case has been prosecuted as involving a seizure disorder rather than an encephalopathy. (ECF Nos. 50, 67.)

Petitioners relied on the opinion of pediatric neurologist Marcel Kinsbourne, M.D. Dr. Kinsbourne's curriculum vitae does not reveal any credentials specific to infantile spasms; however, he testified that in his career he has treated "hundreds" of patients with seizures generally and forty or more patients with infantile spasms in particular. (Tr. 36.) Dr. Kinsbourne considers himself "largely, but not entirely" retired. (Tr. 35.) Petitioners did not offer any opinion from an expert with qualifications specific to immunology.

Respondent filed a responsive expert report by pediatric neurologist John Zempel, M.D., Ph.D (neurobiology). (ECF No. 38-1; Ex. A.) Dr. Zempel is a professor of neurology and pediatrics at Washington University and also has an active clinical practice treating patients with intractable epilepsy wherein he estimates he treats about 10-15 cases of infantile spasms per year. (Tr. 107-09, 112-13.) Dr. Zempel agreed that C.K. suffered infantile spasms but disputed that they were causally related to any of her vaccinations. Respondent likewise did not offer an opinion by an immunologist.

An entitlement hearing was held on July 24, 2017. Maryellen Kottenstette, Dr. Kinsbourne, and Dr. Zempel, all testified. (ECF No. 66, Transcript of Proceedings ("Tr."), 7/24/2017.) Subsequently, a ruling on entitlement was issued on December 12, 2017, finding petitioners entitled to compensation. (ECF No. 78.)

In her ruling, the previously-assigned special master summarized her finding as follows:

> Putting this all together, the undersigned finds that CK, even though she received DTaP, not [DTP],[3] would have qualified to have been in the Bellman and Melchior studies[4] because she had infantile spasms within a week of pertussis vaccination and the vaccination was a trigger, according to both the Bellman and Melchior studies, which prompted the onset of her spasms. We are not dealing with the niceties of statistical significance in the Vaccine Program under the guidance of the Federal Circuit's decisions in *Knudsen*, *Althen*, and *Capizzano*.[5] The principle the Federal Circuit pronounced in *Knudsen*, i.e., that causation can be found in vaccine cases based on epidemiological evidence and the clinical picture regarding the particular child without detailed medical and scientific exposition on the biological mechanisms[,] governs the outcome of this decision.

(ECF No. 78, p. 17.)

Thereafter, the parties resolved the appropriate amount of compensation for the damages in this case over the following year and a half. Respondent filed a proffer on award of damages on May 29, 2019, which the special master adopted as her decision regarding damages. (ECF Nos. 100-02.) The case was reassigned to me on June 5, 2019, and respondent filed a motion for review of the prior ruling on entitlement on June 28, 2019. (ECF Nos. 103, 107.)

On review, the Court of Federal Claims granted respondent's motion and vacated the ruling on entitlement in this case. (ECF No. 130.) The Court found the special master's reliance on the Bellman and Melchior studies to be arbitrary and capricious and also explained that she misapplied the Federal Circuit's *Knudsen* precedent and failed to engage in a full discussion of the type of analysis dictated by the *Althen* precedent.[6] (*Id*. at 6-8.) The Court remanded the case for reconsideration under the

[3] "DTaP" refers to the Diphtheria Tetanus and acellular Pertussis vaccine. "DTP" refers to a different, earlier formulation wherein whole cell pertussis was used. The distinction is further addressed below.

[4] Referring to: M.H. Bellman, E.M. Ross & D.L. Miller, *Infantile Spasms and Pertussis Immunisation*, 1 LANCET 1031 (1983) (Ex. D, Tab 1); J.C. Melchior, *Infantile Spasms and Early Immunization Against Whooping Cough*, 52 ARCHIVES OF DISEASE IN CHILDHOOD 134 (1977) (Ex. D, Tab 2).

[5] Referring to: *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543 (Fed. Cir. 1994); *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274 (Fed. Cir. 2005); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317 (Fed. Cir. 2006).

[6] Notably, the special master's ruling on entitlement did discuss a number of points from prior Federal Circuit precedents having to do with the specifics of petitioners' burden of proof, such as the idea that petitioners are not required to come forward with an exact biological mechanism or that the requirement of epidemiological studies or general acceptance in the scientific community are contrary to the Federal Circuit's *Althen* test. The remanding opinion characterized these points as "well-taken," but concluded that citation to these points does not substitute for the lack of an analysis consistent with the *Althen* test. (ECF No. 130, p. 7.)

correct legal standard, also noting the intervening decision of *Boatmon v. Secretary of Health & Human Services*, 941 F.3d 1351 (Fed. Cir. 2019).

Upon remand, I reviewed the entire record of this case and concluded that the parties had a full and fair opportunity to present their respective cases.[7] Moreover, the remanding opinion did not introduce any issues into the case not previously addressed by the parties in their written submissions. I initially issued a decision on remand dismissing petitioners' case on April 27, 2020. (ECF No. 132.)

Subsequently, however, petitioners moved to reopen the record on entitlement and for reconsideration of my decision. (ECF No. 133.) Petitioners argued that they had not had a full and fair opportunity to present their case, contending, *inter alia*, that the remanding opinion had heightened their burden of proof subsequent to the close of the record on entitlement. (*Id*.) I granted petitioners' motion to the extent of withdrawing the decision on remand to consider petitioners' arguments; however, I denied petitioners' request to reopen the evidentiary record and found the arguments advanced in favor of reconsideration to be unpersuasive. (ECF No. 138.) Accordingly, I indicated that a superseding decision pursuant to Vaccine Rule 10(e) would issue, but that the superseding decision would not reach a conclusion different than the prior, now withdrawn, April 27, 2020 decision on remand. (*Id*.)

Accordingly, the matter is again ripe for decision and, the previously-assigned special master's ruling on entitlement having been vacated, entitlement to compensation in this case will now be considered in light of the guidance provided by the remanding opinion.

II. Applicable Legal Standard

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Additionally, and most significantly, the petitioner must also establish a causal link between the vaccination and the injury.

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[7] In *Kreizenbeck v. Secretary of Health & Human Services*, 945 F.3d 1362 (Fed. Cir. 2020), the Federal Circuit explained that special masters have wide discretion to determine whether oral testimony is reasonable and necessary to resolve the differences in scientific or expert opinion so long as the parties have had a full and fair opportunity to present their case and develop a record sufficient for review. In this case, there has already been a hearing in which expert testimony was presented; however, I was not the special master presiding over this case at that time. Nonetheless, I have reviewed the transcript of that hearing and determined that the testimony provided is sufficient to resolve this case. Notably, the *Kreizenbeck* court explicitly rejected the argument that a special master must hear live testimony before reaching a credibility determination regarding expert opinion. 945 F.3d at 1366.

Where a Table Injury claim is unavailable,[8] the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such cases, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991). The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525.

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

Althen, 418 F.3d at 1278 (citations omitted).

As the remanding order in this case indicated, the Federal Circuit most recently interpreted this causation-in-fact standard in the *Boatmon* case. 941 F.3d at 1351. The *Boatmon* court stressed that "[w]e have consistently rejected theories that the vaccine only 'likely caused' the injury and reiterated that a 'plausible' or 'possible' causal theory does not satisfy the standard. *Id*. at 1360 (citing *Moberly v. Sec'y of Health & Human Servs*., 592 F.3d 1315, 1322 (Fed. Cir. 2010)). Citing to the Circuit's prior *Knudsen* decision, *Boatmon* explained that "[w]hile [the causation-in-fact standard] does not

[8] In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B). In this case, although petitioners initially included a claim of a Table encephalopathy in their petition, by the time of the entitlement hearing they had apparently abandoned that claim. In both their pre- and post-hearing briefs, petitioners asserted that C.K. suffered a vaccine-caused seizure disorder, which is not an injury listed on the Vaccine Injury Table. (ECF Nos. 50, 67.) Additionally, for the reasons discussed in Section VII, below, I have confirmed that C.K. did not experience an encephalopathy within the meaning of the Qualifications and Aids to Interpretation governing the Table Injury of encephalopathy. Accordingly, there is no viable Table claim as originally pled in this case.

require medical or scientific certainty, [a petitioner's theory] must still be 'sound and reliable.'" *Id*. at 1359 (citing *Knudsen*, 35 F.3d at 548-49).

In particular, the remanding order in this case stresses that the language of the Federal Circuit's *Knudsen* decision must be understood in the context of its subsequent *Althen* decision. The remanding order explained that statements in *Knudsen* "should not be taken to loosen the requirements of *Althen*, which was decided almost 11 years later." (ECF No. 130, p. 8.)

III. Issues to be Decided

In this case, there is no dispute that C.K. was properly diagnosed with infantile spasms and that it continues to be her correct diagnosis. (Tr. 54-55 (Kinsbourne), 168-69 (Zempel).) There is also no meaningful dispute that her seizures began soon after her October 2, 2012 vaccinations. (Tr. 38-39 (Kinsbourne), 127 (Zempel).) Rather, the primary dispute between the parties is whether the DTaP vaccine (or any vaccine) can cause infantile spasms in general and whether it did in this case, i.e. issues relating to *Althen* prongs one and two.

In that regard, the question that has so far received the most attention in this case, both in the initial ruling on entitlement and subsequently in the remanding opinion, is the appropriate weight to be assigned to the above-referenced Bellman and Melchior studies. The previously-assigned special master treated these studies as dispositive; however, on review the Court found this to be an abuse of discretion because the special master did not explain the basis for her inference that studies related to the DTP vaccine could provide evidence relative to an injury from the DTaP vaccine.

Significantly, however, the prior special master's conclusion that the Bellman and Melchior studies were dispositive preempted further exploration of the remainder of petitioners' theory pursuant to the *Althen* test. In addition to opining that the DTP-related studies in the record supported petitioners' claim, petitioners' expert also advanced a theory based on an "immune/endocrine model of infantile spasms" whereby he indicated that discharge of proinflammatory cytokines (specifically interleukin 1-β) as part of the innate immune response to vaccination activates the stress system which, in turn, releases a hormone called corticotropin-releasing hormone ("CRH"). According to Dr. Kinsbourne, CRH is known to be epileptogenic. (Ex. 6, pp. 6-9; Tr. 41-42.)

In this decision, familiarity with the prior ruling on entitlement is assumed. Although the previously-assigned special master ultimately relied only on part of the expert presentations in this case, she did discuss each presentation extensively and in full. (ECF No. 78, pp. 4-14.) Accordingly, the expert presentations will not be re-summarized. I will first briefly discuss the injury at issue and clarify the weight and significance of the Bellman and Melchior studies for purposes of determining entitlement in this case. I will then apply the *Althen* test to petitioners' theory of infantile spasms as a form of CRH-induced epilepsy. In applying the *Althen* test in full for the first time in this case, I find that petitioners' proposed theory cannot be meaningfully applied to the

facts of this case and, contrary to the decision previously reached, I conclude that petitioners are not entitled to compensation because they have not met their burden under *Althen* prong two.

IV. C.K.'s Medical History and the Condition at Issue – Infantile Spasms

The condition at issue in this case is not interchangeable with other forms of epilepsy or seizure activity. The condition of "infantile spasms" (also referred to as epileptic spasms or "West Syndrome") was first described in the 19th century. (Tallie Z. Baram, *Pathophysiology of Massive Infantile Spasms: The Putative Role of the Brain Adrenal Axis*, 33 ANN NEUROL 231 (1993) (Ex. 6-1).) The condition represents an epileptic[9] encephalopathy.[10] (Tr. 126.) Outwardly, it is characterized by "repetitive bursts of myoclonic[11] jerking of the head or limbs." (Bellman, *supra*, at Ex. D, Tab 1, p. 1.) However, the three cardinal features of infantile spasms, as explained by both experts in this case, are: (1) encephalopathy; (2) epileptic spasms; and (3) hypsarrhythmia.[12] (Ex. 6, p. 2; Tr. 180-81.)

Infantile spasms typically present between three to nine months of age. (Tr. 123.) The vast majority of cases have onset within the first year of life. (*Id*.) There are "some exceptions, but not many." (Tr. 50.) In some cases, the infantile spasms result from known structural damage in the brain, such as brain damage at birth or encephalitis. (Tr. 49-50.) This is referred to as "symptomatic" infantile spasms. (*Id*.) In contrast, cryptogenic infantile spasms, which may also be called idiopathic infantile spasms, are instances of infantile spasms that have no identified etiology.[13] (Tr. 118-19.)

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[9] According to Dr. Zempel, epilepsy by definition is having more than one seizure that is unprovoked. In most cases, it is not known why an individual seizure occurs when it does. (Tr. 137.) Pertinent to this case, according to Dr. Zempel, C.K.'s "cluster" of seizures represents a single seizure for purposes of assessing the presence of epilepsy. (Tr. 143.) Seizure clusters are a notable feature of infantile spasms. (Tr. 121.)

[10] Broadly speaking, encephalopathy is defined as "any degenerative disease of the brain." (*Dorland's Illustrated Medical Dictionary*, p. 608 (33rd ed. 2019).) With regard to infantile spasms, Dr. Zempel explained that encephalopathy can manifest with immediate signs of an altered mental state such as sleepiness or abnormal behavior or can manifest longer term in the form of developmental regression or stagnation. (Tr. 126-27.)

[11] "Myoclonus" refers to "shocklike contractions of a portion of a muscle, an entire muscle, or a group of muscles, restricted to one area of the body or appearing synchronously or asynchronously in several areas." (*Dorland's*, p. 1205.)

[12] Hypsarrhythmia is "an electroencephalographic abnormality sometimes observed in infants, with random, high-voltage slow waves and spikes that arise from multiple foci and spread to all cortical areas." (*Dorland's*, p. 897.)

[13] I do note that in his post-hearing brief, respondent was critical of Dr. Kinsbourne for using the terms symptomatic and cryptogenic, arguing that the terms are outdated. (ECF No. 74, pp. 14-15.) Respondent filed literature that distinguishes between cryptogenic and idiopathic, proposing that the term cryptogenic should be reserved for cases where an underlying neurological condition, unknown at the time of initial presentation, is subsequently uncovered. (John P. Osborne, *The Underlying Etiology of*

C.K. was born via cesarean section on June 1, 2012, and there is nothing in her own medical records, her mother's preterm medical records, or her delivery records, to suggest her infantile spasms could be symptomatic. There was some discussion during the hearing of whether pregestational diabetes, and Ms. Kottenstette's treatment for that condition with Glyburide, could have contributed to C.K.'s later infantile spasms; however, respondent's expert would not support that contention.[14] (Tr. 154-55.)

On October 2, 2012, C.K. presented for her four-month well baby check. (Ex. 2, pp. 19-22.) No concerns were noted developmentally, neurologically, or in her motor development. (*Id*.) At that time she received several vaccinations, including DTaP, Hib, IPV, and Prevnar. (Ex. 2, p. 21.) Ms. Kottenstette likewise testified that the well-baby check-up was uneventful. (Tr. 8.)

She explained, however, that later that evening while C.K. was nursing "her arms went forward and her head went forward and her legs kind of came up." (Tr. 8.) Ms. Kottenstette explained that her husband made an after-hours call to the pediatrician's office and spoke with a covering pediatrician (i.e. not C.K.'s own pediatrician). (*Id*.) They were advised to take C.K. to the emergency department. At first, petitioners questioned the instruction, explaining that C.K. was not running a fever. According to Ms. Kottenstette, "the physician said that's exactly why you need to bring her." (*Id*. at 8-9.)

Later that night, shortly before 10:00PM, C.K. was taken to the Emergency Department at the University of Massachusetts Children's Medical Center. (Ex. 4.) She was admitted status post immunizations with "abnormal arms [and] shoulder movements multiple times this evening." (*Id*. at 1.) One of these episodes, occurring at about 8:30PM, reportedly lasted about five minutes. (*Id*. at 9.) The episodes did not include eye or leg involvement. (*Id*. at 10.) At the time of evaluation, C.K. was not observed to be in a postictal state. She was also negative for fevers, chills, or fussiness. (*Id*. at 9.) Her initial discharge diagnoses were "rhythmic episode" and "possible seizure." (*Id*. at 5.) A referral was made for a follow up electroencephalogram ("EEG"). (*Id*.)

Infantile Spasms (West Syndrome): Information from the United Kingdom Infantile Spasms Study (UKISS) on Contemporary Causes and their Classification, 51 EPILEPSIA 2168 (2010) (Ex. D, Tab 10, p. 3).) In contrast, the term idiopathic should be used to indicate that no known underlying, predisposing condition is present. (*Id*.) The authors acknowledged, however, that these newly proposed terms are "hardly, if ever, used this way." (*Id*.) Dr. Zempel likewise acknowledged that the older terms are "broadly . . . still in the medical literature." (Tr. 119.) Accordingly, for purposes of this decision, C.K.'s condition is referred to as cryptogenic and references to cryptogenic in the medical literature are generally assumed to constitute cases similar to C.K.'s condition unless otherwise specifically indicated. However, if one accepted the newer terminology, and on the current record, idiopathic would be a more accurate term for C.K.'s condition.

[14] However, Dr. Zempel did note that based on her age at the time of her MRI, cortical dysplasia could still not be ruled out. (Tr. 147-49.)

Ms. Kottenstette explained that she called C.K.'s pediatrician's office the next morning and "spoke with her about what had happened, and we discussed that I should keep an eye on her but that maybe it was a mild reaction to the vaccination or maybe it was reflux.[15] And because it had happened when I was nursing her, I – that made sense that maybe that's what it was." (Tr. 9-10.) Subsequently, however, on October 6, 2012, C.K. experienced another cluster of seizures that was clearly unrelated to nursing. (Tr. 10-11.) Ms. Kottenstette videotaped the seizures and took C.K. to Boston Children's Hospital. (Tr. 11.) C.K. was hospitalized at Boston Children's from October 6 to October 10. (ECF No. 9-1; 9-2.)[16]

Upon admission, C.K. was noted to have experienced three prior clusters of seizures, all of which were described similarly. (ECF No. 9-1, p. 1.) "She woke out of sleep and suddenly had a series of jerks, demonstrated by mom as arms extended out and jerking inward every 5 seconds for about 3-5 minutes. She seemed to be alert throughout the entire episode. Afterwards, she was back to her baseline immediately." (*Id.*) After reviewing the video of the seizure, the admitting physician noted that C.K. "is seen in mom's arms, looking around and appropriately alert, with intermittent episodes of rapid arm extension then shoulder abduction and arm jerk inwards, clinically consistent with infantile spasms." (*Id*.) C.K.'s MRI, echocardiograms, and serum chemistries were negative, but her EEG was consistent with hypsarrhythmia and she was referred to neurology for management of her seizures with a working diagnosis of infantile spasms. (*Id*. at 3, 8.) She was started on ACTH.[17] (*Id*.)

C.K. returned for a neurology follow-up on October 30, 2012. (ECF No. 9-1, p. 10.) Petitioners reported that C.K. experienced some improvement on the ACTH. They reported that the frequency of her spasms increased (from two to three episodes per day to three to five episodes per day), but the duration had decreased to about one to two minutes. (*Id*.) Petitioners confirmed that there had been "no regression in [C.K.]'s development since the spasms began." (*Id*. at 11.) A second EEG did not meet the criteria for hypsarrhythmia, but the diagnosis of infantile spasms was maintained. (*Id*. at 12.) Given her mild improvement with her first course of ACTH, a second course was recommended. (*Id*.) C.K.'s neurological exam was significant for some mildly increased tone in her lower extremities but was otherwise normal and non-focal. (*Id*.)

On November 16, 2012, C.K. had a further neurology follow-up. Her development was still noted to be appropriate and her seizures had decreased in both frequency and severity. (ECF No. 9-1, p. 14.) However, on January 16, 2013, it was noted that she "now seems to be progressively encephalopathic with less movements and arrested development with some elements concerning for regression, particularly

[15] This impression was later memorialized in C.K.'s medical records within the history of present illness provided upon admission to Boston Children's Hospital on October 6. (ECF No. 9-1, p. 1.)

[16] As noted in the prior ruling on entitlement, the records for Boston Children's Hospital were inconsistently labeled as either Exhibit 2 or Exhibit 3, accordingly they will be referenced by their docket location instead.

[17] ACTH is adrenocorticotropic hormone. It is a common treatment for infantile spasms.

her head control and level of interaction." (ECF No. 9-2, p. 4.) Ms. Kottenstette similarly explained during the hearing that C.K. declined very rapidly after her ACTH treatment was stopped after the second round. (Tr. 19-20.)

Ms. Kottenstette testified that, although C.K.'s seizures are not consistent, nothing has eradicated them. (Tr. 15, 17.) C.K. has developed refractory seizures, meaning that they do not respond to medication, and she continues to experience seizures. (ECF No. 9-1, p. 15.) This is unusual in that most children "outgrow" their infantile spasms, leaving her in a smaller category of more severe or prolonged cases. (Tr. 132.) Notably, however, C.K. has not developed any other form of epilepsy, which can sometimes be a further sequela of infantile spasms. (Alexis Arzimanoglou, Renzo Guerrini & Jean Aicardi, *Infantile Spasms and Related Syndromes* (3rd ed. 2004) (Ex. D, Tab 3); Tr. 54-55.) C.K. continued "having approximately 30 seizures a day that last between 10-30 seconds. Her seizures continue to be characterized by epileptic spasms, primarily of the upper extremities and head drops." (Ex. 26, p. 15.) C.K. started going to school and has an IEP in place. (*Id*. at 16.) C.K. had difficulty sleeping, which her neurologist warned may increase C.K.'s frequency of seizure clusters. (*Id*.)

V. Assessing the Melchior and Bellman Studies

Because C.K. developed infantile spasms within one week of her DTaP vaccination, the prior ruling on entitlement treated two studies examining post-DPT infantile spasms – by Melchior and Bellman respectively – as dispositive in this case. (ECF No. 78, pp. 17-18.) On review, that was found to be error because "[t]he special master did not explain the basis of Dr. Kinsbourne's opinion and did not offer an independent basis for applying the DPT-study findings to the DTaP vaccine." (ECF No. 130, p. 6.) In light of this, separate discussion regarding the weight to be given these two studies is warranted.

According to the literature filed in this case, a possible link between pertussis vaccination and infantile spasms was first proposed in 1964. (Melchior, *supra*, at Ex. D, Tab 2, p. 1.) However, subsequent papers suggested that the possible association was merely a coincidence of timing. (*Id*.) In April of 1970, Denmark changed its immunization schedule for pertussis vaccination. Previously, pertussis vaccine was typically administered in Denmark as a triple combination at five, six, and 15 months of age. After April of 1970, that schedule was advanced so that pertussis was administered as a monovalent vaccine at five and nine weeks of age and then again at 10 months. (*Id*.) However, immunization against diphtheria-tetanus-polio was still given at five, six and 15 months of age. (*Id*.) This provided an opportunity to examine whether the change in the vaccine schedule would result in a statistically significant change in the typical age of onset for infantile spasms. (*Id*.) J.C. Melchior published a survey study regarding this question in the Archives of Disease in Childhood in 1977. (*Id.*)

Melchior compared 113 cases of infantile spasms diagnosed between April 1 of 1970 and March 31 of 1975 to 86 cases of infantile spasms occurring from 1957 to

1967. (Melchior, *supra*, at Ex. D, Tab 2, p. 1.) Of the 113 cases from the early 1970's, 40 were classified as cryptogenic, 60 of the subjects as symptomatic, and the remaining 13 reported as having an unclear etiology, but with immunization occurring prior to onset. (*Id*. at 2.) Of those 13 subjects, six had seizures following either the first or second dose of monovalent pertussis and seven had seizures following a combined diphtheria, tetanus, and polio vaccination. (*Id*. (Table 2).) The conclusion reached by the study was that: "A comparison of the age of onset of infantile spasms shows no significant difference between the series of spasms before the new immunization programme and after." (*Id*. at 2.)

Moreover, it was further noted that "[o]f special interest is the occurrence of infantile spasms in 7 children, developing within 2 weeks of the diphtheria-tetanus-polio immunization. This seems to confirm the opinion that we are dealing mainly with a time-coincidence and suggests that whatever immunization we administer in the age groups between 1 and 2 months and 9 and 10 months, some children will develop neurological disorders which are typically associated with these age groups." (*Id.* at 3.) Melchior characterized the possibility of a causal connection between pertussis vaccination and infantile spasms as "very unlikely." (*Id*. at 3.)

Despite these conclusions, Dr. Kinsbourne pointed out certain findings specific to the DTP vaccine. He noted that the Melchior study results demonstrate that "12% of cases of infantile spasms had onset before age 2 months when DTP had not yet been given by then, whereas 23% began before the child was two months old when DTP had been given at 5 weeks. There were nearly twice as many early onsets when DTP had been administered at the earlier age." (Ex. 6, p. 3.)

Critically, however, several prior cases in this program have addressed the distinction between the DTP and DTaP vaccine formulations, the former utilizing whole cell pertussis while the later uses acellular pertussis. These cases have persuasively explained at length why findings relating to the safety of the DTP vaccine are not applicable to the later DTaP vaccine, which was specifically developed to address safety concerns related to the earlier, whole cell DTP formulation. *See, e.g. Sharpe v. Sec'y of Health & Human Servs.*, No. 14-65V, 2018 WL 7625360, at *31-32 (Fed. Cl. Spec. Mstr. Nov. 5, 2018); *Taylor v. Sec'y of Health & Human Servs.*, No. 05-1133V, 2012 WL 4829293, at *30 (Fed. Cl. Spec. Mstr. Sept. 20, 2012); *Holmes v. Sec'y of Health & Human Servs.*, No. 08-185V, 2011 WL 2600612, at *20 (Fed. Cl. Spec. Mstr. Apr. 26, 2011); *Simon v. Sec'y of Health & Human Servs.*, No. 05-941V, 2007 WL 1772062, at *7 (Fed. Cl. Spec. Mstr. June 1, 2007); *Grace v. Sec'y of Health & Human Servs.*, No. 04-[redacted], 2006 WL 3499511, at *9 (Fed. Cl. Spec. Mstr. Nov. 30, 2006). These decisions make clear that epidemiological findings relating to the safety of DTP vaccines cannot reasonably be said to relate to the DTaP vaccine at issue in this case.

In that regard, however, Dr. Kinsbourne testified that efforts to eliminate whole cell pertussis in favor of acellular pertussis are not completely effective:

> As you know, in the acellular vaccine, the pertussis toxin is toxoided, making – hopefully making it unable to bind to the surface of neurons and disable the inhibitory GABA system. That's the point of the toxoid[ing]. However, there is literature, and I think I may have submitted some in the previous case, the *Haynes* matter,[18] which talks about the difficulty of toxoiding all of the pertussis toxin . . . And that is a process which is not perfect. So, one, it may be that the – that there is, in fact, still pertussis toxin in the vaccine, but of course much less because of the toxoiding process . . .

(Tr. 92-93.) Accordingly, Dr. Kinsbourne testified in effect that what is true of the DTP vaccine is also true of the later acellular formulation, but with a lower rate of reaction. (Tr. 57.)

I am not persuaded by this logic. Even if fully crediting Dr. Kinsbourne's assertion that residual pertussis toxin remains in the DTaP formulation, by his own description there remains a difference in formulation that directly implicates vaccine safety and therefore eliminates any possibility of reasonably carrying over statistical observations from one formulation to the other. And since the specific Melchior study findings Dr. Kinsbourne cites are based solely on statistical observation related specifically to incidences following DTP (as opposed to the broader conclusions that do not support petitioners' case), it cannot reasonably be applied in this case, especially in light of the specific history of safety concerns with DTP and the subsequent improvement with DTaP as discussed in the above-referenced decisions. In other words, without more and on this record, Dr. Kinsbourne's intimation of a meaningful residual relationship between DTaP and infantile spasms is entirely speculative.

The subsequent Bellman study, however, presents a more complicated question. In 1983, Bellman et al., published a further study of 269 cases of infantile spasms reported to the National Childhood Encephalopathy Study in Great Britain. (Bellman, *supra*, at Ex. D, Tab. 1, p. 1.)[19] Of those, 92 were classified as symptomatic, 163 as cryptogenic, and a further 14 as "doubtful." (*Id*.) Unlike the Melchior study, Bellman compared the immunized population to age-matched controls. (*Id*. at 2.) Also

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[18] Referring to *Haynes v. Secretary of Health & Human Services*, No. 00-358V, a prior case before the previously-assigned special master. In the prior decision resolving that case, the special master discussed the Bellman and Melchior studies at length and found pursuant to an *Althen* analysis that a DTaP vaccine did cause a child's infantile spasms. 2011 WL 681066 (Fed. Cl. Spec. Mstr. Feb. 7, 2011). During the hearing in this case, the special master explained that she disagrees with the view, as discussed in the above-cited cases, that DTP studies are inapplicable to the later acellular formulation. (Tr. 57.)

[19] Although it was petitioners who sought to rely on this study, citation is to respondent's exhibit. Dr. Kinsbourne cited the 1983 Bellman study in his initial report (Ex. 6, p. 3), but does not actually appear to have included a copy of the study in his submission. Several of the articles cited in his report were omitted, with pages inserted stating only "MISSING TO BE FILED LATER." (*See, e.g.*, Ex. 6, pp. 49, 85.) Nonetheless, Dr. Zempel filed a copy of the Bellman study in support of his rebuttal.

significant, Bellman examined not only the DTP vaccine, but also a DT vaccine without any pertussis at all. (*Id*.)

Examining the pertussis vaccine, the Bellman study found no significant association between spasms and the administration of a pertussis vaccine in either the prior seven days or 28 days. (Bellman, *supra*, at Ex. D, Tab. 1, p. 3.) However, they did find that "a small excess in the number of cases over that expected by comparison with controls in 7 days after immunization with both DTP and DT vaccines followed by a corresponding deficit in the next 3 weeks suggests that, in some cases, immunization may trigger the onset of spasms or attract attention to symptoms in children destined to show the condition overtly within a short time." (*Id*.) Thus, the Bellman study observed a potentially vaccine-related and control-matched change in symptom presentation, albeit a small one.[20] Additionally, unlike the Melchior study, because the same observation was made both among those receiving the DTP and DT vaccines, that finding cannot necessarily be wholly dismissed as relating to the prior whole cell pertussis formulation of the DTP vaccine or to pertussis at all.

Significantly, however, as between the two groups, those experiencing spasms following the DT vaccine were much more likely to be suffering symptomatic rather than cryptogenic infantile spasms. Only about one-third of the post-DT cases were cryptogenic compared to two-thirds of the post-DTP cases. (*Id*. at 3 (Table III).) Dr. Kinsbourne indicated that there is "quite a big difference" between symptomatic and cryptogenic infantile spasms in that symptomatic cases have identified structural damage in the brain. (Tr. 50.) He characterized symptomatic cases as having "extra liability" for a vaccine reaction to occur. (Tr. 60.) Moreover, for his part, Dr. Zempel suggested the uptick in post-vaccination onset observed in the study could be attributable to recall bias, which was also raised by the study authors. (Tr. 161-62.) These factors do cast doubt on the significance of the finding.

For these reasons, I assign no weight to the Melchior study. However, I give some *minimal* weight to the Bellman study as evidence suggesting that onset of infantile spasms may respond to some vaccine formulations involving tetanus and diphtheria and not limited to DTP. However, I do not find that the Bellman study provides evidence specific to the DTaP formulation. Nor, given the above-discussed limitations, do I find that the Bellman study alone is sufficient to provide preponderant evidence of a medical theory linking any vaccine to infantile spasms.

[20] Interestingly, Dr. Zempel filed with his report a 2004 book chapter that noted the Bellman study to be the largest controlled study to date. (Arzimanoglou, Guerrini & Aicardi, *supra*, at Ex. D, Tab 3, p. 15.) Dr. Zempel highlighted language from that chapter explaining that Bellman found the chronological association coincidental; however, the authors also characterized the Bellman study as among studies that "have implicated triple or quadruple immunization as an etiologic factor, with the pertussis component usually being incriminated." (*Id*.)

VI. Applying the *Althen* Test to Petitioners' Claim

a. *Althen* Prong One

Petitioners' burden under the first *Althen* prong is to provide, by preponderant evidence, "a medical theory causally connecting the vaccination and the injury." *Althen*, 418 F.3d at 1278. To satisfy this prong, petitioners' theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548; *Boatmon*, 941 F.3d at 1359. However, such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 549. Scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of Health & Human Servs*., 569 F.3d 1367, 1380 (Fed. Cir. 2009). While special masters may apply the *Daubert* framework[21] to assess expert reliability, special masters are not required to apply *Daubert*.[22] *Boatmon*, 941 F.3d at 1359.

In this case, petitioners' theory seeks to causally link the DTaP vaccine to infantile spasms. As explained above, infantile spasms represent both an epilepsy and a coexisting encephalopathy. Significantly, however, there has been no assertion by Dr. Kinsbourne that C.K.'s vaccinations can be directly linked to the encephalopathy that contributes to C.K.'s infantile spasms. Rather, petitioners contend through their expert that C.K.'s vaccination brought on the onset of her seizures, which, in turn, brought on her condition as a whole. (ECF No. 50, pp. 1, 7; ECF No. 67, pp. 5-6.) Thus, the initial threshold question posed by petitioners' theory is whether vaccination can be considered the trigger of an individual infantile spasm seizure event.[23]

In this regard, Dr. Kinsbourne began with the starting premise that infantile spasms are not wholly genetic in cause, but rather among cryptogenic cases, "[i]nfantile

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[21] When analyzing expert testimony, a *Daubert* analysis weighs the following factors: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community. *See Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 592-95 (1993).

[22] As noted above, in *Boatmon* the Federal Circuit rejected "plausible" or "possible" formulations of expert opinion. 941 F.3d at 1360. In this case, Dr. Kinsbourne in his initial report indicated alternately that his theory is "biologically plausible" or "medically reasonable." (Ex. 6, p. 9.) At the outset of his hearing testimony, he again referenced what is "possible" and what "could" have happened. (Tr. 39.) However, the special master explained that "I can only deal with probable. Possible is irrelevant." (Tr. 37.) She asked Dr. Kinsbourne to clarify his degree of certainty and he ultimately confirmed that regardless of his specific phrasing he holds his opinion "to a medically reasonable degree" and that his opinion is that "the vaccinations probably did cause the onset of her seizures." (Tr. 39-40.)

[23] Dr. Kinsbourne has presented the theory of cytokine-induced seizures in prior cases to mixed results in the recent past. *Compare Jaafar v. Sec'y of Health & Human Servs.*, No. 15-267V, 2018 WL 4519066 (Fed. Cl. Spec. Mstr. Aug. 10, 2018) and *Fuller v. Sec'y of Health & Human Servs.*, No. 15-1470V, 2019 WL 7576382 (Fed. Cl. Spec. Mstr. Dec. 17, 2019).

spasms have been linked to 'stressors that include infections and malformation.'" (Ex. 6, p. 6.) Though he acknowledged that this is believed to be related to age-specific hyperexcitability that constitutes a susceptibility, he further opined that the majority of seizures are not spontaneous, but rather are provoked or triggered by stressful stimuli. (Ex. 6, p. 6 (citing Baram and Hatalski (1998),[24] Brunson (2001),[25] and Dichter (2009)[26]). That is, Dr. Kinsbourne proposed a "two-hit model" of epileptogenesis wherein a susceptibility responds to a stress-related enhancement.[27] (Ex. 6, pp. 6-7.)

More specifically, in 1993, Baram proposed the hypothesis that the endogenous neuropeptide called Corticotripin-releasing hormone ("CRH") acts as a convulsant in the pathophysiology of infantile spasms. (Tallie Z. Baram, *Pathophysiology of Massive Infantile Spasms: Perspective on the Putative Role of the Brain Adrenal Axis*, 33 ANN NEUROL 231 (1993) (Ex. 6-1, p. 1).) This was based on a number of prior observations, including prior evidence that adrenocorticotropic hormone ("ACTH") and glucocorticoids ("GCs") have been effective treatments for infantile spasms as well as evidence from animal studies that showed stress-related increases in CRH synthesis having an effect on the developmental pattern of CRH gene expression. (*Id*. at 2-3.) Baram also observed that a prior study had shown reduced levels of ACTH in the cerebral spinal fluid of infants with infantile spasms. (*Id*. at 4.) Baram confirmed that finding in an age-matched control study as well as a reduction in cortisol; however, no difference was found in CRH levels.[28] (*Id*.) Petitioners cited additional articles by Baram and Hatalski (1998), Brunson (2001), and Dicther (2009), further advancing this hypothesis as a "final

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[24] Tallie Z. Baram & Carolyn G. Hatalski, *Neuropeptide-mediated Excitability: A Key Triggering Mechanism for Seizure Generation in the Developing Brain*, 21 TRENDS NEUROSCI 471 (1998) (Ex. 6-2).

[25] Kristen L. Brunson, Mariam Eghbal-Ahmadi & Tallie Z. Baram, *How do the many Etiologies of West Syndrome Lead to Excitability and Seizures? The Corticotropin Releasing Hormone Excess Hypothesis*, 23 BRAIN DEV 533 (2001) (Ex. 6-4).

[26] Marc A. Dichter, *Emerging Concepts in the Pathogenesis of Epilepsy and Epileptogenesis*, 66 Arch Neurol 443 (2009) (Ex. 6-7).

[27] Notably, in *Boatmon*, the petitioners sought to apply a "triple risk" theory of causation relative to Sudden Infant Death Syndrome that similarly included an underlying vulnerability. 941 F.3d at 1362-63. In that case, petitioners' expert assumed the presence of an underlying brain stem abnormality based on statistical likelihood. *Id*. The Federal Circuit held that in the absence of actual evidence of a brain stem abnormality, a statistical likelihood of such an underlying condition was insufficient to meet petitioners' burden of demonstrating a logical sequence of cause and effect under *Althen* prong two. Unlike in *Boatmon*, however, Dr. Kinsbourne clarified that he did not suggest the presence of an underlying susceptibility as part of his affirmative opinion of cause and effect in C.K.'s case, but only as a means of suggesting why infantile spasms are not more prevalent. (Tr. 51, 88-89.) In fact, he explicitly disclaimed reliance on such a vulnerability, indicating that it "isn't essential to my theory." (Tr. 88.)

[28] This is significant because Baram explained that "[i]n response to a variety of stressful stimuli, the synthesis and secretion of this neuropeptide [i.e. CRH] are increased. CRH acts on the pituitary to promote the release of ACTH, which, in turn, enhances GC synthesis and release from the adrenal. ACTH and GCs act via a negative feedback mechanism to suppress the synthesis and secretion of CRH." (Baram, *supra*, at Ex. 6-1, p. 3.) Accordingly, it does not appear that the findings uniformly supported the hypothesis.

common pathway" that explains the diverse etiologies (i.e. multiple underlying conditions implicated by symptomatic infantile spasms as well as unknown etiologies in cryptogenic cases) of infantile spasms, all of which operate at a specific maturational state present in infancy.

For his part, Dr. Zempel, though he stressed the distinction between a seizure as a unitary event and the overall condition of epilepsy, did not dispute Dr. Kinsbourne's theory that a stressor can trigger a seizure generally. He agreed broadly that stress causes an increase in cortisol (the hormone associated with fight or flight) and that stress "changes the brain" with both short and long-term effects on the structure of the brain.[29] (Tr. 138-39.) He cautioned against thinking of stress as having a "minute-to-minute gating of seizures," and explained that there is much that is not known about why stress can reduce the seizure threshold, but he did agree as a general matter that seizures can be associated with stress, citing examples of students experiencing their first seizures during final exams and anecdotal reports of people experiencing seizures during extreme emotional responses.[30] (Tr. 138-39.) More specifically, Dr. Zempel also agreed that an immune response can lower the seizure threshold, noting in particular that fever is "by far the most powerful component of the immune response that's related to a decrease in seizure threshold." (Tr. 140.) He explained that "[t]here are clearly many processes that are going on that perhaps protect or maybe bring down your defenses at any one moment in time in terms of your propensity for having seizures." (Tr. 141.)

Nonetheless, Dr. Zempel also highlighted a case report by Coppola et al., which followed three sets of identical twins. (Giangennaro Coppola et al., *Case Report: Simultaneous Onset of Infantile Spasms in Monozygotic Twins*, 43 Ped Neuro 127 (2010) (Ex. E); Tr. 150-51.) These case reports noted that in each set of twins, both twins experienced onset of infantile spasms on the same day, despite having had relevant genetic mutations or other known predisposing factors ruled out. (Coppola et al., *supra*, at Ex. E, p. 1.) The authors concluded that these case reports point "to some genetically determined, time-dependent biological factor, apart from any environmental influence."[31] (*Id*. at 4.) Dr. Zempel testified that the report "argues genetics is very

[29] Baram characterized cortisol as "the major human GC." (Baram, *supra*, at Ex. 6-1, p. 4.)

[30] He did caution, however, that "there are not detailed mechanistic studies that say stress causes this, causes this, that then results in a seizure." (Tr. 138.) Dr. Kinsbourne similarly noted in his initial report that "[i]t is quite unknown how stresses interact with the momentary state of a hyperexcitable network to reach a clinical tipping point." (Ex. 6, p. 6.)

[31] Although I agree (as Dr. Zempel testified) that the same-day onset for each pair of twins is striking, this specific statement appears to overstate the significance of these case reports relative to environmental factors. Upon my review of the article, it appears that these twin sets were identified years after onset and, while evidence relating to predisposing factors such as reported family histories and APGAR scores at delivery were explored, I see no discussion to indicate what, if any, measures the authors took to assess the environmental factors existing at the time of onset. In that regard, these remain isolated case reports and one must question how different the environmental influences would be as between the twins in each set of siblings. (For example, pertinent to petitioners' theory, one might expect that infant twin siblings would likely receive their routine vaccinations on the same date.)

powerful in explaining why you have infantile spasms and secondly that it's quite striking that they reported these cases of siblings, identical siblings, who had almost simultaneous onset of their infantile spasms." (Tr. 150-51.) On subsequent questioning, however, Dr. Zempel confirmed that, although infantile spasms "are likely influenced by genetics," he is not of the opinion that infantile spasms are genetically caused. (Tr. 153-54.)

Dr. Zempel also highlighted a 2010 "Consensus Report"[32] on infantile spasms published in *Epilepsia*. (John M. Pellock et al., *Infantile Spasms: A U.S. Consensus Report*, 51 EPILEPSIA 2175 (2010) (Ex. D, Tab 6).) That report explains that "[l]ittle is known about the pathophysiology of [infantile spasms]." However, it also cites approvingly to the Baram hypothesis as one of several hypotheses being explored. (*Id*. at 3.) Both the Consensus Report and Dr. Zempel cautioned that the animal models relied upon in the underlying studies have significant limitations. (Pellock et al., *supra*, at Ex. D, Tab 6, p. 3; Tr. 177-79.) Nonetheless, the Consensus Report also indicated that the nature of infantile spasms is such that "animal models are required to further the understanding of the pathophysiology of [infantile spasms]."[33] (Pellock et al., *supra*, at Ex. D, Tab 6, p. 3.) In any event, that Consensus Report endorsed by Dr. Zempel agrees that trauma, infection, and tumors are known post-natal causes of infantile spasms. (*Id*. at 1.)

Accordingly, it appears on this record that Dr. Kinsbourne's assertion that the stress and immune responses can, in general, trigger a seizure is based on sound and reliable science. This does not, however, specifically implicate vaccinations. Although Dr. Kinsbourne sought in his initial report to explain how the innate immune system – operating via proinflammatory cytokines – interacts with the production of CRH, the contention that vaccination in itself can commence this interaction is based exclusively on Dr. Kinsbourne's *ipse dixit*.[34] The articles discussed above implicate immune

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[32] This Consensus Report was published by 14 authors belonging to various departments of neurology across the United States including, amongst others, John M. Pellock from the Division of Child Neurology at Virginia Commonwealth University School of Medicine, Richard Hrachovy Peter Kellaway Section of Neurophysiology at Baylor College of Medicine, Slomo Shinnar from the Albert Einstein College of Medicine in New York, Tallie Z. Baram from University of California Irvine School of Medicine, David Bettis from Pediatric Neurology of Idaho, and Dennis J. Dlugos from the Children's Hospital of Philadelphia.

[33] Dr. Kinsbourne cited several other animal model studies not specifically discussed herein. (Ex. 6, p. 7.)

[34] In his report, Dr. Kinsbourne wrote: "Spinelli et al (1992) demonstrated that interleukin-6 could enhance production of CRH. In turn, proinflammatory cytokines are released when the innate immune system is activated, by infections and vaccinations. Schmidt et al (1995) showed that even transient activation of CRH production by interleukin 1 could induce long-lasting changes in hypothalamic CRH neurons, rendering the HPA axis hyperresponsive to subsequent stimuli." (Ex. 6, p. 7.) It does not appear that petitioners actually filed either the Spinelli or Schmidt papers referenced in the report, but that is ultimately immaterial. In this report, Dr. Kisnbourne does not attribute to either citation any discussion of vaccination. His insertion of vaccination as the "in turn" vehicle for activation of proinflammatory cytokines, which he intimates are sufficient to bring about the cited findings by Spinelli and Schmidt, are his words alone. In and of itself, that specific statement is not controversial as a question of basic

response to infection, not vaccination, in the onset of infantile spams and Dr. Zempel agreed that fever, not vaccination itself, lowers the seizure threshold. During the hearing, Dr. Kinsbourne was directly asked if any of the literature he filed postulated vaccination as the "second hit" in his two-hit hypothesis. He responded: "Most of the literature speaks about infection. And the study – the animal models clearly show two-hit – two-hit mechanisms. Whether it specifically says vaccination as a second hit I don't recall." (Tr. 78.)

Upon my review, apart from the Melchior and Bellman studies discussed in Section V, above, Dr. Kinsbourne did not purport to provide any evidence in either of his expert reports or his hearing testimony substantiating his assertion that the DTaP vaccine can be the beginning cause of a cascade of inflammation and stress response leading to seizure. Moreover, weighing against that assertion, Dr. Kinsbourne acknowledged that inflammatory cytokine production is a normal part of the vaccine response and is necessary to the efficacy of the vaccine. (Tr. 70.) In his supplemental report he explained that "[t]he innate immune response by [Toll-like Receptor]s, implicating an outpouring of proinflammatory cytokines, is a necessary early stage in the generation of adaptive immunity. *It occurs without negative consequences in the vast majority of cases*."[35] (Ex. 6-A, p. 3 (emphasis added).) In fact, in his supplemental

immunology. However, juxtaposed as the link between his interpretations of the Spinelli and Schmidt studies, it becomes an untested opinion deep-seated in advanced immunology. (In that regard, see also footnote 35, below.) Later in the report, Dr. Kinsbourne seeks further support by discussing more broadly that "[v]accinations activate the innate immune system, which enables adaptive immunity to develop. The activation of Toll-like receptors (TLRs) and the release of proinflammatory cytokines is a necessary condition for the genesis of the adaptive immunity which vaccination is intended to engender." (Ex. 6, p. 7 (internal citations omitted).) It is evident from the face of his report that Dr. Kinsbourne is attempting to stitch together disparate areas of investigation in the field of immunology based only on his own say-so.

[35] The significance of this statement is *not* that Dr. Kinsbourne acknowledges the proposed negative consequences to be rare. This program often addresses rare occurrences. Rather, this statement highlights that Dr. Kinsbourne is relying in the first instance on a normal and expected immune reaction within the human body. In that context, it cannot be enough for Dr. Kinsbourne to merely highlight cytokine production by innate immunity as a process that does occur and thereby claim it to be necessarily injurious. This has been a recurrent issue in cases within this program relative to a number of different conditions. For example, in a case involving sensorineural hearing loss following influenza vaccination, a special master previously and similarly explained:

> the argument that cytokine upregulation can be a pathogenic mechanism unsuccessfully attempts to leverage what is known about how vaccines generally affect the immune system into proof that these anticipated processes can also be pathogenic. To be sure, components of this theory are based on reliable science. Petitioner has referenced reliable literature establishing that certain proinflammatory cytokines (including IL-6 and TNF-alpha) have been shown to be elevated following vaccine administration (*see, e.g.*, Christian at 1, 5), or that these same cytokines may play a role in the process of hearing loss (Kuemmerle-Deschner, Pathak). But the theory lacks similar support for its connecting proposition – that the cytokine upregulation *leads* to or causes hearing loss – as well as the concept that vaccination can instigate the entire disease process. It is not enough to note that increased numbers of inflammatory-associated cytokines have been measured in the context of certain injuries or illnesses (or are involved in the body's reaction to those illnesses). Dr. Axelrod does not personally have demonstrated expertise studying these

expert report, after being challenged regarding the lack of support for his opinion that vaccines can cause infantile spasms, Dr. Kinsbourne conceded that "[i]t is correct that scientific proof is lacking." (Ex. 6, p. 1.) Consistent with this concession by Dr. Kinsbourne, Dr. Zempel denied that vaccines are known in the medical community to be a cause of infantile spasms. (Tr. 160.)

Nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for rev. denied*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. Appx. 999 (Fed. Cir. 2013). Important to this point is Dr. Kinsbourne's lack of any qualifications in immunology. This is not to say he lacks the qualification necessary to opine in this case generally. Neither expert in this case is an immunologist and the injury at issue is neurologic, squarely within both experts' field even if some of the known or suspected causes intersect with other disciplines. Moreover, some inferences grounded in sound and reliable science may be appropriate. However, petitioners are specifically theorizing an immunologic cause of a neurologic condition and bear the initial burden of proof on this point. In this instance, Dr. Kinsbourne's lack of relevant qualification coupled with the quality of his testimony specific to this case, leave unpersuasive his unsupported extrapolation beyond the well-established aspects of immunology. In fact, Dr. Kinsbourne was candid in acknowledging during the hearing that certain aspects of his theory were beyond his expertise.[36] (Tr. 96-99.)

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unsupported elements of the theory, and no persuasive or reliable literature was offered on such points.

Inamdar v. Sec'y of Health & Human Servs., No. 15-1173V, 2019 WL 1160341, at *17 (Fed. Cl. Spec. Mstr. Feb. 8, 2019); *see also Bender v. Sec'y of Health & Human Servs*., 141 Fed. Cl. 262, 266 (2019) (denying a motion for review where "[t]he Special Master found that Dr. Byers cited no evidence to explain how the mere presence of cytokines could instigate an autoimmune process that results in a demyelinating condition in the central nervous system ("CNS"), particularly when the vaccines were injected in the periphery."); *McKown v. Sec'y of Health & Human Servs*., No. 15-1451V, 2019 WL 4072113, at *50 (Fed. Cl. Spec. Mstr. July 15, 2019) (finding with regard to eczema that "[t]he fact that cytokine upregulation is promoted by vaccination – a medically reliable assertion standing alone – does not mean that this cytokine increase is definitionally *harmful*, especially given (as observed by Dr. MacGinnitie) that it is difficult to establish whether certain proinflammatory cytokines are instigators or merely mediators of a disease process begun in some other way."); *Palattao v. Sec'y of Health Human Servs*., No. 13-591V, 2019 WL 989380, *36 (Fed. Cl. Spec. Mstr. Feb. 4, 2019) (explaining that "[p]etitioners argued that the immunologic stimulation that vaccinations generally provide (which inherently encourage cytokine production) could result in a demyelinating condition like TM. Petitioners' theory was rooted in the general proposition that virtually *any* vaccine could be pathogenic and result in TM. *See* Tr. at 160. But they have offered insufficient reliable scientific or medical evidence that addresses the specific pathogenicity of the vaccines in dispute herein, nor anything connecting vaccines to TM based merely on their recognized pro-inflammatory capacities.").

[36] During the hearing respondent's counsel asked Dr. Kinsbourne if he was of the opinion that infantile spasms are an autoimmune condition. He responded that by virtue of his proposed theory, they are. (Tr. 96.) In follow up, the special master questioned the accuracy of that assertion. She asked "now, what are

Accordingly, while I find that Dr. Kinsbourne's broader assertion that a seizure can be triggered by an immune-related or stress-related response to infection or trauma is sound and reliable, the further, more specific assertion that a vaccination can itself act as that stressor without other factors of stress or inflammation is largely unsupported on this record. Only scant evidence from the Bellman study supports the idea that any vaccine, let alone the DTaP vaccine particularly, can cause a temporal shift in the onset of infantile spasms. Thus, although I accept for purposes of a theory of general causation that vaccines can in some contexts contribute to seizures as part of a larger immune/inflammatory process, namely where as Dr. Zempel acknowledged the vaccine causes a seizure threshold-reducing fever and thereby results in febrile seizures, I do not find preponderant evidence on this record that the DTaP vaccine itself can cause seizures. Therefore, I end the *Althen* prong one analysis here, because this distinction has case-dispositive implications, discussed below, for petitioners' case under *Althen* prong two.[37]

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the cytokines attacking in particular? The brain is normal on MRI, so what substance in the body is the cytokine attacking in order to have this autoimmune response?" (Tr. 98.) In response, Dr. Kinsbourne testified that cytokines "increase the excitation level of neurons" and that "an excess of proinflammatory cytokines via the microglia can cause excitotoxic damage and actually kill a neuron, or at the lower level can excite neurons enough to cause seizure discharges." (Tr. 98-99.) The special master sought further clarification, asking "[i]sn't this immune-mediated, not autoimmune?" Dr. Kinsbourne responded that he is not aware of the distinction, adding "perhaps I should be, but I'm not." This prompted the special master to reconfirm Dr. Kinsbourne's earlier acknowledgment that he is not an expert in immunology before further suggesting "[s]o maybe you shouldn't be answering this question." Dr. Kinsbourne replied "[i]t becomes more apparent now." (Tr. 99.)

[37] In point of fact, the question of whether vaccination can trigger a seizure is only a threshold question raised by petitioners' theory. Since the condition of infantile spasms constitutes an epileptic encephalopathy, the question of the trigger for the first seizure is not the end of the analysis. Dr. Zempel persuasively explained that:

> We have to distinguish between the process of having epilepsy, which is epileptogenesis, and the idea that you may have a seizure, which is a unitary event. So epilepsy is when you've had more than one seizure of unknown cause. So, for example, a stressor loosely defined or a fever, more precisely defined, in general is not -- does not then lead to a diagnosis of epilepsy unless there are seizures that occur in the absence of those stressors. So if I get hit in the head with a baseball bat and have a seizure, that doesn't qualify as epilepsy.

(Tr. 141-42.) Accordingly, even if a vaccine could trigger a seizure, the next question would be what relationship, if any, that vaccine-induced seizure has to the overall course of infantile spasms. That is, could a single vaccine-induced seizure be theorized to represent a substantial contributing factor in causing the condition of infantile spasms? For all the reasons discussed in Section VI(b), below, it is not necessary to reach that question.

I do note, however, that in the course of this case, Dr. Kinsbourne at least briefly touched upon three potential answers to that question. First, he proposed that each seizure itself has a destructive effect on the brain, perhaps suggesting an argument that any given seizure contributes to the child's coexistent encephalopathy. (Tr. 48-49.) Second, he opined that the process described by his theory results in glutaminergic and excitotoxic changes in the brain which themselves enhance susceptibility to subsequent seizures, suggesting an argument that a first, vaccine-induced seizure has a causal relationship to all the subsequent and cumulatively damaging seizures. (Tr. 98-99.) And finally, and most

b. *Althen* Prong Two

The second *Althen* prong requires preponderant evidence of a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e., as opposed to the question of general causation posed by the first prong, the question is whether the vaccine (or vaccines) actually caused the alleged injury in the case at hand. *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1345 (Fed. Cir. 2010) ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case . . . ."); *Pafford v. Sec'y of Health & Human Servs.,* 451 F.3d at 1352, 1355-56 (Fed. Cir. 2006) (accepting the special master's can it/did it formulation as equivalent to *Althen* prongs one and two).

In this case, when asked for the basis of his opinion that C.K.'s own vaccination caused her infantile spasms, Dr. Kinsbourne initially explained that his opinion was based on the apparent temporal association and offered no other evidence of cause and effect explaining C.K.'s own condition. (Tr. 38-40.) Pressed further, he indicated that the fact that C.K. experienced a clear and decisive onset of not just one seizure, but a cluster of seizures, suggested that a definite event happened to trigger those seizures.[38] (Tr. 44-45.) On later cross-examination, however, Dr. Kinsbourne again indicated that his opinion was based exclusively on a temporal association: "I'm offering this as a reasonable medical mechanism. I'm not offering it as scientific certainty. It is reasonable to suppose that when the onset of the seizure disorder is within hours of a vaccination that the – and when the vaccination is known to produce proinflammatory cytokines, which are known to have an excitatory or even repligenic property that the – that property of the cytokines was involved in the onset of the seizure disorder." (Tr. 73.)

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fully addressed, Dr. Kinsbourne opined that the timing of onset of infantile spasms dictates, or at least influences, the severity of the sequela. Accordingly, he opined that by triggering the first seizure earlier in life, a vaccination can advance the onset of infantile spasms and necessarily make the condition worse than it otherwise would have been. (Tr. 52-53, 58-59.)

Dr. Zempel disputed that the timing of onset dictates prognosis. He acknowledged that in general there is a tendency for more severe cases to manifest earlier, but he explained that those cases tend to be instances of symptomatic infantile spasms. He indicated that more than anything else the underlying cause of the infantile spasms determines outcome. (Tr. 130-34.) His testimony regarding the impact of seizures, however, was more nuanced. Dr. Zempel cautioned that infantile spasms encompass both a seizure disorder and an encephalopathy and that "[t]he key characteristic [of infantile spasms] is that the encephalopathy is out of proportion to the expected cause of problems by the seizures." (Tr. 127-28.) He further explained that seizures in infantile spasms are treated less aggressively than other types of seizure activity. (Tr. 127-28.) However, when directly asked by the special master whether in cases of infantile spasms it is the seizure activity or the encephalopathy that damages the brain, he responded "I think it's both." (Tr. 127.) He also testified that "[i]f you've had a meningitis or encephalitis or an infection or particularly prenatal infections . . . it's like a chicken-or-the-egg issue in many cases. You know, these infections may cause developmental genetic changes that involve genes." (Tr. 153-54.)

[38] Dr. Zempel testified, however, that seizure clusters are a common presentation that distinguishes infantile spasms from other forms of epilepsy. (Tr. 120-21.)

This type of mere suspicion of a temporal relationship is not sufficient to establish causation. "When a petitioner relies upon proof of causation in fact rather than proof of a Table Injury, a proximate temporal association alone does not suffice to show a causal link between the vaccination and the injury . . . A reputable medical or scientific explanation must support this logical sequence of cause and effect." *Grant v. Sec'y of Health & Human Servs*., 956 F.2d 1144, 1148 (Fed. Cir. 1992) (citing 42 U.S.C. § 300aa–13(a)(1)). There is some inconclusive suggestion in the record of this case that the course of C.K.'s infantile spasms responded to treatment with ACTH. (ECF No. 9, pp. 11-13; Tr. 12; Ex. 6, p. 6; Ex. A, p. 5.) As noted above, Dr. Kinsbourne cited the efficacy of ACTH treatment for infantile spasms as supportive of the hypothesis that seizures may have a stress hormone-related pathophysiology. (Ex. 6, p. 6.) However, even if I were to accept this as some limited evidence that C.K.'s initial seizures were triggered or mediated by a stress hormone, this relates only to the broadest aspect of Dr. Kinsbourne's theory and, without more, does not implicate C.K.'s vaccination(s) as a relevant stress event. Consistent with Dr. Kinsbourne's above-cited testimony, I can find no other evidence in the record supporting the assertion that C.K.'s DTaP vaccine, or any other vaccine, did cause her infantile spasms.

As described above in reference to petitioners' theory, Dr. Kinsbourne acknowledged that inflammatory cytokine production is a normal part of the vaccine response and is necessary to the efficacy of the vaccine and "occurs without negative consequences in the vast majority of cases." (Tr. 70; Ex. 6, p. 3.) In that regard, Dr. Zempel suggested that evidence of inflammation, such as MRI findings or fever, would be expected if excessive or abnormal cytokine inflammation were the cause of C.K.'s condition. (Tr. 173-75.) Moreover, as Dr. Zempel explained, fever is "by far the most powerful component of the immune response that's related to a decrease in seizure threshold." (Tr. 140.) However, at the time she first presented with symptoms later diagnosed as infantile spasms, C.K. was observed to be alert and active. She was also negative for fevers, chills, or fussiness. (Ex. 4, p. 9-10.) Ms. Kottenstette also confirmed in her testimony that C.K. was afebrile at the time of onset. (Tr. 8-9.)

Dr. Kinsbourne disagreed with the suggestion that cytokine inflammation would necessarily manifest clinically beyond C.K.'s seizures. (Tr. 99-100.) Asked if there is otherwise any evidence to suggest C.K. had a cytokine reaction, he indicated that "[t]here is nothing in her personal file that deals with this matter. It was not investigated. It would take – it's not a routine investigation that's usually done." (Tr. 100.) Unfortunately, however, even accepting this at face value, this leaves petitioners with only a circular argument – the seizures themselves are advanced as the only available evidence of the alleged, underlying inflammation that is argued to be the manner by which the vaccine can be shown to have caused the seizures.[39]

[39] Additionally, the reasonable limits of the clinical investigation in C.K.'s case cut both ways. Dr. Zempel observed that additional imaging would be necessary to completely rule out cortical dysplasia, which may not have been visible on C.K.'s MRI at the time. (Tr. 147-48.) This condition is not typically visible on MRI until about 24-40 months of age. (Tr. 148; Pellock et al., *supra*, at Ex. D, Tab 6, p. 5.)

In contrast, where Dr. Kinsbourne's theory was previously accepted, there were complex, febrile seizures involved, which were outwardly suggestive of an inflammatory reaction and significant enough to be identified as the catalyst for more seizures. *Fuller v. Sec'y of Health & Human Servs.*, No. 15-1470V, 2019 WL 7576382 (Fed. Cl. Spec. Mstr. Dec. 17, 2019). These factors are not present in this case. In this case, there is no evidence that C.K.'s seizures were focal, complex, or febrile. (Tr. 55, 146, Ex. 4, pp. 9-10; ECF No. 9, p. 1.) And, although infantile spasms can secondarily lead to other forms of epilepsy (Arzimanoglou, Guerrini & Aicardi, *supra*, at Ex. D, Tab 3, p. 27-28), petitioners contend that cryptogenic infantile spasms, rather than any other form of epilepsy, remained the correct diagnosis at the time of the hearing.[40] (Tr. 54-55.)

Additionally, there is not preponderant evidence from any of C.K.'s treating physicians attributing her condition of infantile spams to her vaccination. Following her initial emergency department presentation, Dr. Catherine Riordan, C.K.'s pediatrician, suggested in follow-up the possibility that C.K. was experiencing a mild vaccine reaction; however, the basis for that opinion was not explained. (Tr. 9-10; ECF No. 9-1, p. 1.) Moreover, at the time, it appears that Dr. Riordan may not even have recognized C.K.'s convulsions as seizures or, at the very least, was not yet committed to that diagnosis. Ms. Kottenstette testified that she was initially told that "maybe it was a mild reaction to the vaccination or maybe it was reflux." (Tr. 9-10.) C.K.'s discharge diagnoses from the night prior had been "rhythmic episode" and "*possible* seizure." (Ex. 4, p. 5 (emphasis added).) In that regard, Dr. Zempel testified that one of the difficulties in diagnosing infantile spasms "is that it can be very complicated in the beginning when the spasms are much more subtle to really understand what they are." (Tr. 124.) He noted that early seizures can be mistaken for reflux, twitches, or myoclonus. (Tr. 125.)

This lack of outward clinical evidence implicating C.K.'s vaccination as a cause of her seizures presents an especially challenging obstacle for petitioners in this case, because both experts otherwise agree that infantile spasms have a known, age-related onset even without any known or well-established trigger. As noted above, Dr. Zempel testified that infantile spasms typically present between three to nine months of age. (Tr. 123.) The vast majority have onset within the first year of life. (*Id*.) Dr. Kinsbourne agreed, noting that there are "some exceptions, but not many." (Tr. 50.) Moreover, Dr. Kinsbourne suggested in his initial report that this onset relates to "an age specific hyperexcitable network." (Ex. 6, p. 6 (quoting Frances Jensen, *Relationship Between Encephalopathy and Abnormal Neuronal Activity in the Developing Brain*, 49 ACADEMIC PRESS 23 (2002) (Ex. 6-12)).) Having suffered onset of her infantile spasms following her four-month well exam, C.K. was squarely within this age range. Accordingly, the evidence of record not only fails to present affirmative evidence of a logical sequence of

[40] At the hearing, Dr. Kinsbourne testified that he had personally observed C.K. seizing the night before. (Tr. 54.) The special master asked "So is it your testimony that she doesn't have partial complex or any other seizures; she still has infantile spasms?" He answered "I specifically looked for any other seizure type, and I asked the parents. And I didn't locate any." (Tr. 54-55.)

cause and effect linking vaccination to injury, it also suggests there is reason to doubt the significance of the apparent temporality.[41]

Nonetheless, Dr. Kinsbourne opined that C.K. was not preordained to experience infantile spasms, and had she not had a trigger (her vaccines in this case), she would have had an opportunity to exit the apparent age-related risk window. (Tr. 52-53.) Dr. Kinsbourne did not agree that everyone who develops epilepsy is predisposed to it, noting, for example, that some epilepsies follow head trauma. (Tr. 75.) In his initial report, however, he explained this point in greater detail and revealed why this line of reasoning does not support petitioners' claim. He wrote:

> Would [C.K.] not have developed infantile spasms at all but for the four-months vaccinations? Would she necessarily have encountered another stress capable of triggering infantile spasms in the remaining temporal window of susceptibility up to the age of eight months? It is quite unknown how stresses interact with the momentary state of a hyperexcitable network to reach a clinical tipping point. *At this time, this question is unanswerable*. But any claim that she was "predestined" to suffer from this disease to this degree (or at all) would be speculation. Predestination is not provided for in medical science. At the very least, the vaccine injury deprived her of the chance to emerge unscathed from the temporal window of risk.

(Ex. 6, p. 6. (emphasis added).) Having acknowledged himself that the question is unanswerable due to the limits of our understanding of how stress interacts with the body to reach a clinical "tipping point" – that is, that he cannot affirmatively say that C.K. could have exited the risk window "but for" these vaccinations – he attributes speculation only to the presumed counterpoint. However, petitioners must initially come forward with evidence showing a logical sequence of cause and effect demonstrating that the vaccination did cause C.K.'s injury. Absent that showing, the significance of the temporal relationship remains unsubstantiated regardless of whether I accept that the infantile spasms would have inevitably occurred anyway.

Finally, Dr. Kinsbourne also devoted much of his presentation to opining that, statistically speaking, if C.K. had experienced seizures later in life, they would not have taken as damaging a form, since the most severe epilepsies develop in the first year of life. (Tr. 59, 76.) However, this point goes to the further consideration of whether one vaccine-induced seizure led to further sequela and contributed significantly to C.K.'s

[41] In their post-hearing brief, petitioners argue that Dr. Zempel conceded that DTaP can cause seizures "in a few cases." (ECF No. 67, p. 7 (citing Tr. 136).) This is incorrect. Dr. Zempel did not agree that DTaP can cause seizures in a few cases. He agreed that the authors of the Melchior paper made that assertion. (Tr. 135-36.) However, for the reasons discussed in Section V, above, I am assigning no weight to the Melchior study. Moreover, Dr. Zempel's testimony was clear that his opinion is that the age-specific onset of infantile spasms "complicates whether there is a causal relationship because temporal correlation does not imply causation. And simply by the tens of millions of people who obtain routine vaccinations as part of their medical care by necessity, a small number of children who are going to present with infantile spasms have those spasms present in a time period around the time where they got vaccinations." (Tr. 134.)

overall condition. Absent a demonstration that any one seizure was triggered by her vaccination in the first place, this line of reasoning is moot.[42]

For these reasons, I find that petitioners have not satisfied *Althen* prong two.

c. *Althen* Prong Three

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11–355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

Both Dr. Kinsbourne and Dr. Zempel explained that it is very difficult to determine the true onset of infantile spasms. (Tr. 70, 124-25.) Many families recognize early signs only in hindsight. (Tr. 125.) In this case, however, both experts reasonably assumed that onset occurred approximately ten hours following C.K.'s October 2, 2012 vaccinations. (Tr. 38-39, 127.) This is the point at which C.K.'s family first became concerned and, as Dr. Zempel described it, "whether something was going on before that is unknowable at this point." (Tr. 127.) Although he suggested that insidious onset is more common, Dr. Zempel characterized an abrupt onset as "not an atypical case either" and explained that he takes the abrupt onset suggested by the medical records "at face value." (Tr. 170.)

Dr. Kinsbourne, while acknowledging he is not an immunologist, indicated that, based on his review of relevant literature, the innate immune response he cites as part of his theory would occur "very fast, as a matter of hours."[43] (Tr. 62-63.) When asked whether onset of infantile spasms within one day of vaccination was medically reasonable in light of Dr. Kinsbourne's opinion that C.K.'s injury was brought about by her innate immune reaction, Dr. Zempel declined to answer. (Tr. 170-71.) He stressed

[42] Notably, this also is not uncontested. Dr. Zempel disagreed that age of onset is related to outcome. (Tr. 131-33.) He also disagreed with the assertion that, but for the timing of her onset, C.K. was necessarily positioned for an optimal recovery. (Tr. 165-68.)

[43] According to the literature filed in this case, and as the term "trigger" may suggest, the time from stress event to seizure is rapid (within minutes). (Baram & Hatalski, *supra*, at Ex. 6-2, p. 2.) Accordingly, the overall temporal relationship at issue is largely determined by the innate immune reaction cited by Dr. Kinsbourne as inciting the stress event rather than by the endocrine aspects of the theory.

that he is not an immunologic expert and indicated that since he disagreed that vaccine-causation is even possible, he could not identify what would be medically reasonable.[44] (*Id*.)

For purposes of this decision, since it is unrebutted, I accept Dr. Kinsbourne's opinion that onset of seizures within ten hours of vaccination is medically reasonable in light of his proposed theory. In a prior case, Dr. Kinsbourne explained in greater detail that his theory expects seizures to occur within three days of vaccination, a period that is consistent with the time-frame identified for onset of a Table encephalopathy (which may include seizures) following DTaP vaccination. *Fuller*, 2019 WL 7576382, *7; 42 C.F.R. § 100.3. In that prior case, Dr. Kinsbourne cited literature illustrating that among Vaccine Adverse Event Reports with a known interval between vaccination and seizure, one third (11 out of 33) experienced seizures on the same day as vaccination. *Fuller*, 2019 WL 7576382, *7 (citing M. Miles Braun et al., *Infant Immunization with Acellular Pertussis Vaccines in the United States: Assessment of the First Two Years' Data from the Vaccine Adverse Event Reporting System (VAERS)*, 106 PEDIATRICS 1 (2000)). Notably, this is also consistent with the observations in the Bellman study that onset of infantile spasms following DTP vaccination was reported to be as little as less than 24 hours and that there was a reported increase in incidences of infantile spasms within seven days of both DTP and DT vaccination.[45] (Bellman, *supra*, at Ex. D, Tab 1, p. 2.)

For these reasons, I find that petitioners have satisfied *Althen* prong three.

VII. Table Encephalopathy

Petitioners initially pled this case as a Table encephalopathy. (ECF No. 1.) Additionally, both experts in this case have explained that the cardinal characteristics of infantile spasms include the presence of an encephalopathy. (Ex. 6, p. 2; Tr. 180-81.) Accordingly, in the interest of completeness, I note that the Qualifications and Aids to Interpretation for a Table encephalopathy require, within 72 hours of vaccination, an *acute* encephalopathy which, following a seizure, presents as "a significantly decreased

[44] Although I appreciate the logic behind Dr. Zempel's answer, especially in light of my discussion with regard to *Althen* prong one, I do not find this testimony to be fully satisfactory in the context of this case. Dr. Kinsbourne's explanation of his theory should have been sufficient for Dr. Zempel to engage with the theory's underpinnings notwithstanding his ultimate disagreement. That is, Dr. Zempel would not have had to concede the validity of the theory to raise *additional* faults related to timing if he had identified any. Accordingly, the true significance of Dr. Zempel's testimony appears to be that he does not have the immunological background necessary to refute Dr. Kinsbourne's assertion. Similarly, in his expert report, Dr. Zempel asserted that Dr. Kinsbourne's opinion that a one-day onset is consistent with an innate immune response was "not 'medically reasonable'" based only on the fact that Dr. Kinsbourne did not provide a specific citation for that assertion. He did not offer any explanation for why Dr. Kinsbourne may be incorrect.

[45] I stress that for all the reasons discussed in Section V, above, the Bellman study does not provide evidence that the DTaP vaccine can cause infantile spasms; however, I did find that it provided some minimal evidence that the DTP and DT vaccines triggered seizures in some children later diagnosed with infantile spasms. Accordingly, it does provide some evidence relating to the expected temporal relationship between seizures and vaccines generally.

level of consciousness that lasts at least 24 hours and cannot be attributed to a postictal state—from a seizure or a medication." 42 C.F.R. § 100.3(b)(2)(i)(2). Upon my review of the complete record, there is not preponderant evidence that C.K. experienced an acute encephalopathy consistent with the requirements of the Vaccine Injury Table. In particular, Dr. Zempel persuasively explained:

> [T]he encephalopathy associated with infantile spasms is that the child isn't right. They're sleeping too much; they're not reacting normally. The testimony I heard was that it took many weeks for – for the medical caregivers to really notice that an encephalopathy or developmental detail or stagnation had occurred, most prominently after withdrawal of the ACTH. So I think there are some children who have immediate signs that they're just not right associated with the seizures. Many children have the epileptic spasms preceding the development of this longer – longer range developmental delay or developmental stagnation.

(Tr. 126-27.)

VIII. Conclusion

It is readily apparent that C.K. and her family have experienced a tragedy. My sympathies extend to them all. However, in light of the above-discussed legal standards that must be applied in this and in all cases in this program, I cannot conclude that C.K.'s infantile spasms were vaccine-caused. Although the onset of C.K.'s infantile spasms appears temporally related to her vaccination, there is not preponderant evidence that the vaccination did cause her condition. Unfortunately, for all of the reasons discussed above, I must therefore conclude that petitioners are not entitled to compensation and this case is **DISMISSED**.

Pursuant to Vaccine Rule 28.1(a), the clerk of court is directed to notify the assigned judge of the filing of this decision on remand. In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court is directed to enter judgment accordingly.[46]

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master

[46] Entry of judgment can be expedited by each party's filing of a notice renouncing the right to seek review. Vaccine Rule 11(a).